REMARKS

Status of the claims

Claims 1-9, 11, 12, 15, 17-25, 34, and 36-43 are pending and under consideration in this application. All the pending claims stand rejected.

35 U.S.C. §112, first paragraph, rejection

Claim 34 stands rejected on the grounds that the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

From the comments on page 2, line 23, to page 6, line 8, of the Office Action,Applicants understand the Examiner's position to be that the specification is enabling for a method of treating hematopoietic tumors and metastatic tumors but that it is not enabling for a method of treating localized non-hematopoietic tumors.

Applicants disagree with this position. Indeed, in the experiment described in Example 6, the tumor treated was a localized primary tumor in the flanks of the experimental animals. Since the targeting cells were injected intravenously, in order to access the solid tumor they presumably had to migrate via the circulatory system to the site of the tumor, traverse relevant blood vessels and then enter the solid tumor in order to mediate their effect.

With reference to issue of hematopoietic versus non-hematopoietic tumors, Applicants acknowledge that there are significant differences in the biology of the two tumor types. However, with respect to the ability of targeted immunotoxins to kill tumor cells, there is no biological difference between the two tumor types that Applicants are aware of that would make it easier to kill hematopoietic tumor cells in general than non-hematopoietic tumor cells in general. Applicants submit that any problems in a particular immunotoxic therapy regimen are likely to be due to variables such as the potency of the toxin, toxicity to the host subject, and a lesser degree of access of immunotoxins to solid tumors in general than to disseminated tumors in general, rather than to whether the tumor is of hematopoietic or non-hematopoietic origin.

Moreover, Applicants respectfully submit that, in view of the experiments of the inventors showing a significant therapeutic activity against a localized leukemia (Example 6 of the instant application) and a disseminated leukemia (Declaration of March 27, 2002), one of skill in the art would conclude that the methodology used in the experiments would likely have a similar degree of therapeutic benefit against solid and disseminated tumors in general and that the success of the experiments was not likely due to both the localized and the disseminated tumors being of hematopoietic origin. If the Examiner has evidence to believe that immunotoxic therapy of the type claimed in the present application is likely to be more effective on hematopoietic tumors (solid and disseminated) than on non-hematopoietic tumors (solid and dessiminated), she is requested to provide such evidence.

The single note of doubt in the Cochlovius et al. article in regard to adoptive transfer of *in vitro* activated effector cells is made with reference to the effector cells being the only mediators of tumor cell death. The paper describes transduction of the effector cells with a vector expressing CD44 in order to facilitate increased homing of the effector cells to melanoma cells in the skin. However, the article makes no mention of transducing effector cells with nucleic acids expressing immunotoxins of any sort, let alone those employed in the instant invention. The targeting cells of present invention act both as delivery vehicles for tumor cell-killing immunotoxins as well as tumor cell killers *per se*. One of skill in the art would consider it very likely that far fewer immunotoxin-secreting effector cells are required to kill tumor cells at a particular site than effector cells whose efficacy is due soley to their own cytotoxic activity. Indeed the experiments described in Example 6 and the Declaration of March 27, 2003, indicate this to be the case.

In light of the above considerations, Applicants respectfully submit that claim 34 is enabled with respect to localized as well as disseminated tumors, regardless of whether is the tumor is of hematopoietic or non-hematopoietic origin, and therefore request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

35 U.S.C. §112, second paragraph, rejections

Claims 1-9, 11, 12, 15, 17, 18-25, 34, and 36-38 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention.

Applicants respectfully submit that, in light of the amendment (replacing "pathogenic" with "cancer") to claim 1, which is supported by the specification (e.g., at page 6, lines 19-24), the rejection on page 6, lines 16-17, of the Office Action is moot.

Applicants have amended claim 34 to clarify that the "subject with cancer" recited in the preamble and in the positive step of the claim ("administering said cell population of claim 22 to said subject") contains the cancer cell for which the targeting cell is specific and on the surface of which the second member of the affinity pair is expressed (as specified by claim 1 to which claim 22 refers). Applicants respectfully submit that, in light of this amendment, the rejection on page 6, lines 18-19, of the Office Action is moot.

Applicants submit that the rejection on page 6, lines 20-22, of the Office Action is moot in light of the amendment to claim 36, which is supported by the specification, e.g., at page 4, lines 13-18; and page 36, line 28, to page 37, line 32.

Applicants have amended claim 38 to refer to the appropriate antecedent ("said nucleic acid") in the claim. Applicants respectfully submit that, in view of this amendment, the rejection on page 7, lines 1-2, is moot.

No new matter is added by any of the above amendments.

In light of the above considerations, Applicants respectfully request that the rejections under 35 U.S.C. §112, second paragraph, be withdrawn.

35 U.S.C §103(a) rejections

(a) Claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25, and 36-42 stand rejected as allegedly being unpatentable over Paul et al. (U.S. Patent No. 5,736,387; the '387 patent), in view of Chan et al., Debinski et al., and Chen et al. Applicants respectfully traverse this rejection.

From the comments on page 7, line 25, to page 10, line 25, of the Office Action, Applicants understand the Examiner's position to be that the '387 patent teaches all aspects of the instant invention other than a cytokine-toxin construct and that this embodiment is taught by the other cited art. Applicants disagree with this position.

Claims 1, 2, 4-6, 8, 9, 11, 12, 15, 17-25, 36, and 37

The invention of the '387 patent is a means for directing genes to desired target cells. Retroviral vectors containing coding sequence of interest are linked to chimeric targeting proteins (CTP) containing two domains, the first of which serves to bind the vector-CTP complex to target cells of interest and the second of which serves to facilitate entry of the vector-CTP complex into the target cell (e.g., Abstract). Not only does the '387 patent fail to mention cytokine-toxin constructs, it more importantly contains no mention of T cells (with significant binding affinity for a cancer cell) transduced with a vector expressing such a construct. The reference to TIL in the '387 patent occurs in the context of a discussion of the uses of retroviruses in general (starting in column 25, line 60). The text cited by the Examiner refers to studies of others in which TIL (in addition to other hematopoietic cells) were transduced with retroviral vectors expressing a detectable marker in order to track the migration of the TIL after injection into cancer patients (column 26, lines 7-30). There is no teaching, or even the remotest suggestion, in the '387 patent that the retroviral vectors with which the TIL are transduced contain inserts encoding anything other than a detectable marker. In particular, there is not the least suggestion in the '387 patent that: (a) coding sequences in retroviral vectors transduced into TIL encode a cytokine alone or a toxin alone, let alone a fusion protein containing both; or (b) that TIL be used for the delivery of anything, let alone such a fusion protein.

The reference in the '387 patent to the use of a toxin molecule when T cell is suppression desired is in the context of a description of cells that can be targeted by the retrovirus-CTP constructs (column 26, line 31, to column 27, line 16). This teaching is entirely unrelated to the use of retroviral vectors for tracking the fate of TIL and other hemaopoietic cells (see above). Thus the relevant section of the '387 patent indicates that a retrovirus-CTP complex in which the

CTP targets the complex to a T cell can be used to deliver a coding sequence in the retrovirus encoding toxins to T cells in order to suppress unwanted proliferation of the T cells. This text does not teach, or even make the slightest suggest of, a T cell with significant binding affinity for a cancer cell containing a vector expressing any protein, let alone the fusion protein embodied by the instant claims.

In summary, the '387 patent fails to teach a T cell with significant binding affinity for a cancer cell containing a vector expressing the fusion protein of the instant claims. This deficit in the '387 patent is not remedied by any of the other cited references which similarly fail to disclose such a cell transduced with any vector, let alone one expressing the fusion protein of the instant claims. Debinski et al. and Chan et al. disclose immunotoxins composed of cytokine genes and toxins and vectors expressing them. They make no mention of any isolated mammalian cells transduced with such vectors, let alone a T cell with significant binding affinity for a cancer cell. As pointed out in the response filed April 3, 2003, the targeting cell used in Chen et al. is not one with significant binding affinity for a cancer cell and there is no suggestion in the reference of the desirability of such a cell.

Claims 38-42

As detailed above, the '387 patent is directed to targeting of retroviral vectors to a wide variety of mammalian cells in order to obtain expression of coding sequences in the retroviral vectors by the mammalian cells. There is no disclosure, or even a suggestion, of a retrovirus expressing a nucleic acid sequence encoding an immunotoxin of any sort, let alone those described by the other cited art. Thus, the '387 patent lacks motivation to combine its disclosure with that of any of the other references.

Chen et al. discloses a retrovirus expressing an immunotoxin composed of a single chain Fv fragment and a toxin (page 78, column 2, paragraph 3). There is no disclosure, or even a suggestion in Chen et al. of using anything other than a sFv (e.g., a cytokine) as a targeting domain. Thus, Chen et al. provides no motivation to combine its disclosure with either Debinski

et al. or Chan et al. and thus to make a retroviral immunotoxin in which targeting domain is a cytokine.

In addition, even if there was motivation to combine their disclosures, the combination of the '387 patent and Chen et al. lacks, and contains no suggestion of, what Chen et al. lacks, i.e., immunotoxins containing cytokines as targeting domains.

Debinski et al. and Chan et al. describe plasmid vectors only for use in bacterial production of immunotoxic proteins, which are then used for *in vitro* experiments only (Debinski et al.) or for both *in vitro* and *in vivo* experiments (Chan et al.). There is no disclosure, or even a suggestion of the desirability, of transforming mammalian cells with any viral vector expressing an immunotoxic protein, let alone a retroviral vector. For example, neither reference suggests using gene therapeutic methods (*in vivo* or *ex vivo*) of delivering immmunotoxins to appropriate subjects. Thus, neither reference contains the motivation to look for an expression vector other than a plasmid in which to insert sequences encoding their immunotoxin. Hence, neither Debinski et al. nor Chan et al. provides the requisite motivation to combine its disclosure with that of the '387 patent and/or Chen et al. and thus make retroviral vectors that express the immunotoxins that Debinski et al.and Chan et al. disclose.

Thus, none of the cited references, considered alone or in combination, disclose or even suggest the invention of the instant claims.

(b) Claims 3 and 7 stand rejected as allegedly being unpatentable over Paul et al. (U.S. Patent 5,736,387; the '387 patent), in view of Chan et al., Debinski et al., and Chen et al., and further in view of Cochlovius et al. Applicants respectfully traverse this rejection

From the comments on page 11, lines 6-22, of the Office Action, Applicants understand the Examiner's position to be that Cochlovius et al. supplies what is missing from the other cited art with respect to claims 3 and 7. Applicants disagree with this position.

As indicated above, none of the '387 patent, Chan et al., Debinski et al., and Chen et al., either singly or in combination, render claim 1 obvious because none disclose, or even suggest the desirability of, transducing cells with significant binding affinity for cancer cells with

a vector of the instant invention. While Cochlovius et al. discloses transducing effector cells (cytotoxic T lymphocytes; CTL) specific for a melanoma antigen, the transduced coding sequence is not one encoding a protein with tumor cell killing activity, let alone an immunotoxin described by Chan et al., Debinski et al., or Chen et al.. The coding sequence (encoding the homing receptor CD44) transduced in Cochlovius et al. serves merely to improve the homing capacity to skin of CTL not producing any exogenous cytotoxic molecule. There is no teaching, or even the slightest suggestion of the desirability, of transducing CTL with a vector expressing an immunotoxin of any kind, let alone one described in either Debinski et al. or Chan et al. Thus, Cochlovius et al. contains no motivation to combine its disclosure with that of Chan et al. or Debinski et al.

Moreover, even if there was the necessary motivation in Cochlovius et al. to combine its disclosure with that of Chen et al., or vice versa, which, for the same reasons given for Chan et al. and Debinski et al., there is not, neither reference discloses the immunotoxic fusion proteins used in the present invention (i.e., those in which the targeting domain is a targeting molecule other than antibody or antibody fragment).

Finally, the combination of Cochlovius et al. and the '387 patent lacks disclosure of transduction of any cell, let alone one with significant binding affinity for a cancer cell, with a coding sequence encoding the immunotoxin of the present invention.

It should be pointed out that, even if the combination of references were to render one or more of the instant claims obvious, while Cochlovius et al. discloses tranduction with vector expressing a cell adhesion receptor (CD44), not an immunotoxin in which the targeting domain is ligand for a cell adhesion receptor as specified by claim 3. This consideration provides an additional indicium of non-obviousness for claim 3 over Cochlovius et al.

In light of the above considerations, none of the cited references, singly or in combination, renders claims 3 and 7 obvious.

(c) Claim 43 stands rejected as allegedly being unpatentable over Paul et al. (U.S. Patent 5,736,387; the '387 patent), in view of Chan et al., Debinski et al., and Chen et al., and further in

view of Clay et al. or Buchsbaum et al. (U.S. Patent No. 6,001,329; the '329 patent). Applicants respectfully traverse this rejection.

From the comments on page 12, lines 7-22, Applicants understand the Examiner's position to be that, in mentioning viral vectors, Clay et al. or Buchsbaum et al. provide what is missing from the other cited art and thus, in combination with that art, render claim 43 obvious. Applicants disagree with this position.

Applicants note that Clay et al. was accepted for publication on January 16, 1999. The priority date of the instant application is May 26, 1999. Thus, Applicants do not acknowledge that the reference is necessarily prior art with respect to the instant application. However, even if it is prior art, for the reasons given below, it does not, either alone or in combination with the other cited references, render claim 43 obvious.

For the reasons given above, none of the '387 patent, Chan et al. and Debinski et al., singly or in combination, render viral vector claims 38-42 obvious. Clay et al. describes experiments with retroviruses expressing T cell receptor genes and designed to generate CTL with specificity for a melanoma cells (e.g., Abstract). There is no disclosure, or even suggestion, in Clay et al. that such retroviruses express the tumor cytotoxic molecules of any sort, let alone the immunotoxins of Chan et al. and Debinski et al. In the background section of the Clay et al., there is a overview of various viral vectors and their respective advantages and disadvantages. While there is a listing of various coding sequences (including those encoding cytokines) that can be used in such viral vectors for gene therapy purposes (Table 2), there is no teaching, or suggestion of the desirability, of such sequences encoding immunotoxins of any sort, let alone those employed by Debinski et al. or Chan et al. Thus, Clay et al. contains no motivation to combine its disclosure with that of Chan et al. or Debinski et al. and to make viral vectors expressing their respective immunotoxins. In addition, since Chan et al. and Debinski et al. provide no reason to use any vectors other than plasmid vectors (see above), they do not provide the motivation to combine their disclosure with that of Clay et al.

In that neither Chen et al. nor Clay et al. discloses or suggests the use of non-antibody targeting domains in immunotoxins, the combination of the two references fails to render

obvious the viral vectors of the instant invention. The same is true for the combination of the '387 patent and Clay et al.

Buchsbaum et al. describes the production and use of radiolabeled immunotoxins containing a cytokine, a toxin, and a radionuclide (e.g., Abstract). However, Buchsbaum et al. does not teach the use of viral vectors expressing any immunotoxin, let alone those of Chan et al. or Debinski et al. The only context in which Buchsbaum et al. mentions viral vectors (adenoviral vectors) is for creating cancer cells transduced with genes expressing either an experimental antigen of interest (e.g., carcinoembryonic antigen) (columns 19-20) or a cytokine receptor to which the reference's radiolabeled immuntoxins containing corresponding cyokine targeting domains can bind (columns 35-36). Since the reference is concerned only with the administration of radiolabeled protein immunotoxins, not surprisingly it neither discloses nor even suggests an adenoviral vector expressing any immunotoxin, let alone those of Chan et al. or Debinski et al. Thus, Buchsbaum et al. contains no motivation to combine its disclosure with that of Chan et al. or Debinski et al. In addition, since Chan et al. and Debinski et al. provide no reason to use any vectors other than plasmid vectors (see above), they do not provide the motivation to combine their disclosure with that of Buchsbaum et al.

In that neither Chen et al. nor Buchsbaum et al. discloses or suggests the use of non-antibody targeting domains in immunotoxins, the combination of the two references fails to render obvious the viral vectors of the instant invention. The same is true for the combination of the '387 patent and Buchsbaum et al.

In light of the above considerations, none of the cited references, singly or in combination, render claims 43 obvious.

In view of the above factors, Applicants respectfully request that the rejections under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

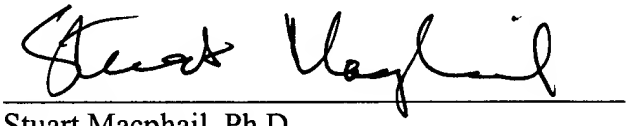
In summary, for the reasons set forth above, Applicants maintain that all of the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a petition for an automatic extension of time and check in payment of the extension of time. Please apply any additional charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 11983-004001.

Respectfully submitted,

Date: 11/3/03



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